B2

22. (Amended) The method of claim 20, wherein said antiviral protein conjugate or said antiviral peptide conjugate comprises (i) an amino acid sequence of SEQ ID NO: 2 or a mutant thereof, and (ii) an isolated and purified viral envelope glycoprotein.

REMARKS

The Present Invention

The present invention is directed to a method of inhibiting therapeutically or prophylactically a viral infection of a host. The method comprises administering to the host an antiviral effective amount of an isolated and purified antiviral agent selected from the group consisting of an antiviral protein, an antiviral peptide, an antiviral protein conjugate, and an antiviral peptide conjugate, wherein the antiviral protein or antiviral peptide has an amino acid sequence of SEQ ID NO: 2 or a mutant thereof whereupon administration of the antiviral effective amount of the antiviral agent, the viral infection of the host is inhibited.

The Pending Claims

Claims 20-27 are currently pending and are directed to the method of inhibiting therapeutically or prophylactically a viral infection of a host.

Amendments to the Claims

Claims 20 and 22 have been amended to point out more particularly and claim more distinctly the present invention. The amendments to claims 20 and 22 are supported by the instant specification at, for example, page 14, line 32, through page 15, line 4. No new matter has been added by way of these amendments. Separate documents setting forth the precise changes to the claim as well as the text of all pending claims are enclosed herewith.

Examiner Interview

Applicant wishes to thank Examiner Parkin for the courtesy of the telephonic interview of December 18, 2001. Applicant is most appreciative of the Examiner's time in discussing the matters set forth in the Office Action and herein with Applicant's representative Heather R. Kissling.

The Office Action

The Office has rejected claims 20-27 under 35 U.S.C. § 112, first paragraph. Claims 20 and 21 have been provisionally rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 20-24 of Application No. 09/428,275. Claims 20 and 21 have been further rejected under the

judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 13-19 of U.S. Patent No. 6,015,876. Reconsideration of these rejections is hereby requested.

Discussion of Rejection under 35 U.S.C. § 112, first paragraph

Claims 20-27 have been rejected under Section 112, first paragraph, for alleged lack of enablement. This rejection is traversed for the reasons set forth below.

The Office contends that the instant specification provides insufficient guidance as to which regions of the cyanovirin peptide (i.e., which fragments of at least nine contiguous amino acids of SEQ ID NO: 2) are required for antiviral activity (Office Action, Sections 1-3). It appears that the rejection is centered on the phrase "at least nine contiguous amino acids of SEQ ID NO: 2." Solely in an effort to advance prosecution of the instant application, the pending claims have been amended to recite that the antiviral protein or antiviral peptide has an amino acid sequence of SEQ ID NO: 2 or a mutant thereof, as suggested by the Examiner in the telephonic interview of December 18th.

The antiviral peptide or antiviral protein of the present inventive method is completely enabled and adequately described in the instant specification. Applicant provides nucleic acid and amino acid sequences encoding cyanovirins in SEQ ID NOS: 1-4 and Figure 2, for example. Generating mutations in the nucleic acid or amino acid sequence to produce a mutant cyanovirin coding sequence that encodes a functional antiviral peptide or antiviral protein is described in the instant application at, for example, page 14, line 32, through page 15, line 4. As required by the pending claims, the amino acid sequence of SEQ ID NO: 2 or the mutant thereof has antiviral activity. Methods of screening candidate proteins and peptides for antiviral activity are provided in the instant specification at, for example, page 24, line 19, through page 25, line 25, and in Examples 5 and 6. Specifically, Example 5 provides a method for determining a candidate peptide's ability to inhibit the cytopathic effects of a virus, HIV-1, upon human cells, while Example 6 provides a method to determine the ability of a candidate peptide to interrupt cell-virus binding. The methods involve routine laboratory techniques that are well within the skill of the ordinary artisan.

Moreover, Applicant has generated mutants of SEQ ID NO: 2, which have mutations at one, two or three amino acid residues and which retain antiviral activity, as described in the Rule 132 Declaration of Dr. Michael R. Boyd submitted herewith. Indeed, the spectrum of antiviral activity of the generated cyanovirin mutants against representative clinical isolates of HIV-1 was essentially the same as wild-type cyanovirin. In addition, according to Dr. Boyd, one of ordinary skill in the art has the requisite knowledge and ability to generate further mutations (e.g., ten mutations) in SEQ ID NO: 2 to obtain mutants of SEQ ID NO: 2

retaining antiviral activity. For example, the three-dimensional structure of the cyanovirin peptide can be obtained on the amino acid sequence of SEQ ID NO: 2. The ordinarily skilled artisan, upon mapping the topological conformation of the peptide, can determine which amino acid residues can be manipulated while not disrupting peptide folding. Likewise, it is understood in the art that surface hydrophobicity is responsible for protein-protein interactions. The ordinarily skilled artisan can map hydrophobicity surface clusters on the cyanovirin peptide to determine which amino acid residues can likely be manipulated such that hydrophobicity characteristics of these clusters are essentially unchanged. Thus, using the specification as a guide, one of ordinary skill in the art can make and use the present invention with routine experimentation.

The Office also contends that, given the unrelatedness of enveloped viruses, it is unlikely that cyanovirins would be capable of binding to viruses other than HIV-1, thereby inhibiting a viral infection. As set forth in the Rule 132 Declaration submitted August 6, 2001, Applicant has, indeed, demonstrated that cyanovirins are capable of binding viruses other than HIV. Using routine methods (e.g., ELISA and affinity chromatography) that were readily available before 1995, it has been demonstrated that cyanovirins bind viral surface glycoproteins other than gp120 of HIV, namely the surface glycoprotein gp1-Z of the Ebola virus and the gC glycoprotein of the virus *Herpes simplex* (HSV). It has been further demonstrated that cyanovirins are able to bind to the carbohydrate moieties of viral surface glycoproteins from which the proteinaceous component has been removed. Thus, it is reasonable for the ordinarily skilled artisan to expect that cyanovirins can bind a wide array of pathogens, such as viruses, comprising surface carbohydrate moieties, such as glycoproteins.

Moreover, it is reasonable to predict that the binding of cyanovirins to the viral glycoproteins described in the Rule 132 Declaration submitted August 6, 2001, would effectively inhibit infection of host cells by those viruses. As set forth in the Rule 132 Declaration of Dr. Michael R. Boyd submitted herewith, gp-1Z of Ebola and gC of HSV are responsible for the initial virus-cell contact required for viral infection, which is similar to the role of gp120 in HIV infection. Therefore, it is reasonable to predict that the binding of cyanovirins to these glycoproteins, like the inactivation of HIV by binding of cyanovirins to gp120, will attenuate infection of viruses other than HIV.

The Office further contends that the working examples of the instant application are not sufficient to enable the pending claims, and that the experiments described in the Declaration Under 37 C.F.R. § 1.132 submitted February 1, 2001, do not accurately predict inhibition of a viral infection therapeutically or prophylactically (Office Action, Section 6).

First, the ability of the presently claimed method to inhibit therapeutically or prophylactically a viral infection in a host has been demonstrated *in vivo* using a clinically

relevant animal model and using the guidance provided in the instant application. Indeed, cyanovirin successfully inhibited viral infection in a macaque animal model, as described in the Rule 132 Declaration submitted February 1, 2001. The dose of virus that was effectively blocked from infecting the animal subjects was *known to produce 100% infectivity* in macaques via the route of administration utilized, i.e. the dose of virus was physiologically relevant. Therefore, the data provided demonstrate that the antiviral agent of the present inventive method achieves the claimed biological effect, namely inhibition of a viral infection.

Second, the animal model described in the Rule 132 Declaration is a clinically relevant model and reasonably predictive of success in inhibiting viral infection. The Office contends that the animal model used is not predictive of clinical results, and cites Rice and Bader (1995) in support of its contention. Yet, Rice and Bader (1995) is solely directed to *in vitro* assays and does not discuss any *in vivo* models, much less the macaque model described in the Rule 132 Declaration. Moreover, one of the references previously cited by the Office, namely Allan (Chapter 1.2, *AIDS: Biology, Diagnosis, Treatment and Prevention,* fourth edition, DeVita et al., Eds., Lippincott-Raven Publishers (1997)), characterizes the macaque animal model as "an important animal model" (page 15, 1st col.). Allan further states that models using SHIV can be used to determine "whether the animal is protected from infection as determined by virus isolation, antibody responses, and detection of viral DNA in tissues by polymerase chain reaction" and that recombinants between HIV and $SIV_{smm/mac}$ "are reasonable choices in the design of such experiments" (page 23, 2nd col., lines 1-7).

Third, the Office contends that the Rule 132 Declaration submitted February 1, 2001, is deficient in that it failed to measure reductions in viral load. However, the pending claims are directed to a method of inhibiting a viral infection of a host. The results described in the Rule 132 Declaration of February 1, 2001, demonstrate that cyanovirins successfully inhibited a viral infection due to inoculation of SHIV89.6P intrarectally or intravaginally, respectively. All treated animals were protected from viral infection, as demonstrated by the absence of viral isolates and viral DNA in blood samples. Thus, in view of the absence of viral isolates, measurement of viral load was not appropriate, and the ability of the antiviral peptides and antiviral proteins of the present inventive method to inhibit a viral infection has been proven.

Finally, the ability of the antiviral agent of the present inventive method to inhibit therapeutically or prophylactically a viral infection in a host has been demonstrated in a mouse model of Ebola virus-induced hemorrhagic fever. As set forth in the Rule 132 Declaration of Dr. Michael R. Boyd submitted herewith, three groups of mice were inoculated with a dose of Ebola virus known to produce 100% infectivity in the mouse

model. Group 1 was administered a dose of CV-N one day prior to inoculation through five days post-inoculation (day 5). Group 2 animals were administered CV-N eight hours post-inoculation through day 5. Control animals (Group 3) were inoculated with virus but were not treated with CV-N.

Due to the highly infectious nature of Ebola virus, isolation of viral isolates and determination of viral load is not possible. Accordingly, the ability of CV-N to inhibit viral infection was evaluated based on survival of treated animals versus control animals. All control animals expired by day 7. The administration of CV-N following viral inoculation prolonged survival of Group 2 mice three days as compared to controls. The administration of CV-N before Ebola virus inoculation extended survival of 100% of Group 1 mice to day 9, with 80% of mice surviving to day 11, the last timepoint observed. CV-N prevented the onset of symptoms of Ebola virus infection throughout the course of its administration and significantly delayed the lethal effects of the virus after administration of CV-N was stopped in both prophylactic and therapeutic *in vivo* models. Accordingly, the ability of the present inventive method to inhibit therapeutically or prophylactically a viral infection has been proven.

For the reasons set forth above, the presently claimed invention is enabled by the instant application. Accordingly, Applicant requests withdrawal of the rejection under Section 112, first paragraph.

Discussion of Provisional Obviousness-Type Double Patenting Rejection

Claims 20 and 21 have been provisionally rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 20-24 of Application No. 09/428,275. This rejection will be addressed upon indication of allowable subject matter.

Discussion of Obviousness-Type Double Patenting Rejection

Claims 20 and 21 have been rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 13-19 of U.S. Patent No. 6,015,876 ("the '876 patent"). This rejection is believed to be moot in view of the terminal disclaimer, submitted herewith, disclaiming that portion of the term of any patent that issues on this application beyond that of the '876 patent.

Conclusion

The application is considered to be in good and proper form for allowance, and the Examiner is respectfully requested to pass this application to issue. If, in the opinion of the

Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned attorney.

Respectfully submitted,

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